Notice of Allowability	Application No.	Applicant(s)	
	09/830,227	TIMMERS ET AL.	
	Examiner	Art Unit	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment of 01-09-04*.

2. ☒ The allowed claim(s) is/are *1-6 and 10-13*.

3. ☐ The drawings filed on _____ are accepted by the Examiner.

4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☒ Other *"Allowable Subject Matter"*.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mr. Mark W. Milstead on 03-30-04.

The application has been amended as follows:

Claim 1: amend as in the attachment.

Claims 3-6: amend as in the attachment.

Cancel claims 7-9.

Claim 10: amend as in the attachment.

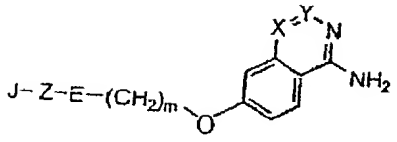
Add claims 11 and 12: as in the attachment.

Also add,

Claim 13: An anticoagulant composition, comprising: the serine protease inhibitor according to claim 1, and a pharmaceutically acceptable carrier or excipient.

In the Claims

1. (Currently Amended) A serine protease inhibitor having the formula (I),

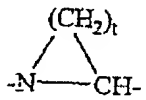


in which

J is H, R^1, R^1-O-C(O)-, R^1-C(O)-, R^1-SO_2-, R^3OOC-$(CHR^2)_p$-, $(R^{2a},R^{2b})N$-CO-$(CHR^2)_p$- or Het-CO-$(CHR^2)_p$-;

Z is an amino-acid of the formula -NH-CHR^1-C(O)-, -NR^4-$CH((CH_2)_qC(O)OR^1)$-C(O)-, -NR^4-$CH((CH_2)_qC(O)N(R^{2a},R^{2b}))$-C(O)-, -$NR^4$-$CH((CH_2)_qC(O)Het)$-C(O)-, D-1-Tiq, D-3 Tiq, D-Atc, Aic, D-1-Piq, ~~D-3 Piq~~ D-3-Piq, glutanyl or a (C_1-C_6) alkylester thereof;

E is -NR^2-CH_2- or the fragment



, which is unsubstituted or substituted with (1-6C)alkyl, (1-6C)alkoxy or benzyloxy;

R^1 is selected form (1-12C)alkyl, (2-12C)alkenyl, (2-12C)alkynyl, (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl, (1-6C)alkoxy, oxo, OH, CF_3 or halogen, and

from (6-14C)aryl, (7-15C)aralkyl, (8-16C)aralkenyl and ~~(14-20C)(bisaryl)alkyl~~ (14-20C)(bisaryl)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy, OH, CF_3 or halogen;

R^2, R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (3-8C)alkenyl, (3-8C)alkynyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen, and from (6-14C)aryl and (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen;

R^3 is the same as R^2 or is Het-(1-6C)alkyl;

R^4 is H or (1-3C)alkyl;

X and Y are CH or N, with the proviso that they are not both N;

Het is a 4-, 5- or 6-membered heterocycle containing one or more heteroatoms selected from O, N and S

m is 1 or 2;

p is 1, 2 or 3;

q is 1, 2 or 3;

t is 2, 3 or 4;

Tiq is 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

Atc is 2-aminotetraline-2-carboxylic acid;

Aic is 2-aminoindan-2-carboxylic acid; and

Piq is 1-perhydroisoquinolyl carboxylic acid;

or a pharmaceutically acceptable addition salt or solvate thereof.

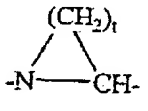
2. (Previously presented) The serine protease inhibitor according to claim 1, wherein m is 2; X is CH and Y is CH.

3. (Currently Amended) The serine protease inhibitor according to claim 2, wherein

J is H, R^1 R^1-SO_2-, R^3OOC-$(CHR^2)_p$-, $(R^{2a},R^{2b})N$-CO-$(CHR^2)_p$- or Het-CO(CHR^2)p-;

Z is an amino-acid of the formula -NH-CHR^1-C(O)-, -NR^4-$CH((CH_2)_qC(O)OR^1)$-C(O)-, -NR^4-$CH((CH_2)_qC(O)N(R^{2a},R^{2b}))$-C(O)-; ;

E is -N(3-6C)cycloalkyl-CH_2- or the fragment



, which is unsubstituted or substituted with (1-6C)alkyl or 1-6C)alkoxy;

R^1 is selected from (1-12C)alkyl, (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl, (1-6C alkoxy or oxo, and from (6-14C)aryl, (7-15C)aralkyl and (14-20C)(bisaryl)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy OH, CF_3 or halogen;

R^2 is H;

R^{2a} and R^{2b} are each independently selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and ~~(3-6C)cycloalkyl(1-4C)alkylene~~ (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy and from (6-

14C)aryl and (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen;

R^3 is selected from H, (1-8C)alkyl, (3-8C)cycloalkyl and (3-6C)cycloalkyl(1-4C)alkylene, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen and from Het-(1-6C)alkyl;

p is 1;

q is 2;

t is 3 or 4.

4. (Currently Amended)) The serine protease inhibitor according to claim 3, wherein

Z is an amino-acid of the formula $-NH-CHR^1-C(O)-$ or glutamyl or an (1-6C)alkylester thereof;

R^1 is selected from (3-12C)cycloalkyl and (3-12C)cycloalkyl(1-6C)alkylene, which groups are unsubstituted or substituted with (3-12C)cycloalkyl or (1-6C)alkoxy, and from (6-14C)aryl, (7-15C)aralkyl and ~~(14-20C)(bisaryl)alkyl~~ (14-20C)(bisaryl)alkyl, wherein the aryl groups are unsubstituted or substituted with (1-6C)alkyl, (3-12C)cycloalkyl, (1-6C)alkoxy or halogen; and

R^3 is selected from (1-8C)alkyl and (3-8C)cycloalkyl, which are unsubstituted or substituted with (3-6C)cycloalkyl or (1-6C)alkoxy, and from (7-15C)aralkyl, wherein the aryl groups are

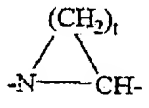
unsubstituted or substituted with (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, CF_3 or halogen and from Het-(1-6C)alkyl.

5. (Currently Amended) The serine protease inhibitor according to claim 4, wherein

J is $-CH_2COO$(1-6C)alkyl, (3-8C)cycloalkyl, $-SO_2$-10-camphor, $-CH_2CONH$phenyl or $-CH_2CONH$(3-8C)cycloalkyl

Z is D-cyclohexylalaninyl, D-phenylalaninyl, D-diphenylalaninyl or glutamyl, or an (1 6C)alkylester thereof; and;

E is the fragment



, wherein t is 3 or 4.

6. (Currently Amended) A pharmaceutical composition comprising the serine protease inhibitor of claim 1 and at least one pharmaceutically suitable ~~auxillary~~ auxiliary.

7-9. (Cancelled)

10. (Currently Amended) A method of ~~effecting~~ inhibiting coagulation by serine ~~protease~~ proteases ~~inhibition~~ in the blood coagulation cascade in a mammal, comprising:

administering to the mammal an effective amount of a serine protease inhibitor according to claim 1.

11. (New) A method for treating a thrombin-mediated and thrombin-associated disease in a mammal, comprising:

administering an effective amount of the serine protease inhibitor according to claim 1.

12. (New) The method according to claim 11, wherein the thrombin-mediated and thrombin-associated diseases are selected from the group consisting of deep vein thrombosis, pulmonary embolism, thrombophlebitis, arterial occlusion from thrombosis or embolism, arterial reocclusion during or after angioplasty or thrombolysis, restenosis following arterial injury or invasive cardiological procedures, postoperative venous thrombosis or embolism, acute or chronic atherosclerosis, stroke, and myocardial infarction.

Allowable Subject Matter

The attached Examiner's amendment has placed the instant application in condition for allowance by inserting names for the abbreviations of Tiq, Atc, Aic, Piq, and clarifying the method claims. New claims 11-13 are drawn to more specific methods of treatment and composition.

Claims 7-9 are cancelled.

With no other outstanding rejection, claims 1-6 and 10 are allowed along with new claims 11-13.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M-T (~10 am ~ 8:30 pm) starting from February 22nd, 2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached at 571-272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting SPE of 1624, at 571-272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

RICHARD L. RAYMOND
PRIMARY EXAMINER
ART UNIT 1624

T. Truong
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March 30, 2004